REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated May 14, 2008. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 36-39 and 41 - 68; stand for consideration in this application, wherein claims 1-35, 40, stand canceled without prejudice or disclaimer, while claims 45 -66 stand withdrawn and claims 36 and 68 are being amended to more particularly point out and distinctly claim the subject matter of the invention.

Claim Objections

Claim 36 stands objected for a clerical error. Said clerical error has been corrected. Withdrawal of this ground for objection is respectfully requested.

Rejections under 35 U.S.C. 112, First Paragraph

Claims 36 – 39, 41-44, 67, and 68 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly incorporating new matter for reference to "cartilaginous matrix" and "bone matrix." The Examiner alleges that the Applicants are attempting to shift the focus of the invention and that the said terms are not universally accepted.

Applicants respectfully disagree with the Examiner on the grounds that it is a well settled and within ready grasp of one of skill in the art that osteoblasts secret osteoid matrix (bone matrix) and chondrocytes secrete cartilaginous matrix and these cells exist within said matrix. Use of said terms is ordinary and quite trite in this art area and the Applicants do not believe that their use is any way amounts to new matter. The Examiner is respectfully requested to see page 5, paragraphs 2 and 3 of the Specification where the Applicants specifically defined the terms "cartilaginous substance" and "bone substance" in a manner that is clearly consistent with generally understood meaning of "cartilaginous matrix" and "bone matrix' respectively. Nevertheless, in order to advance the prosecution of this Application, Applicants have amended the claims accordingly and respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 36 – 39, 41-44, 67, and 68 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because the process steps of claim 36 do not include the use of "chondroblasts," 'cartilaginous matrix," "osteoblasts," or "bone matrix." The Examiner alleges that it is not clear how the steps in the product-by-process limitations appear to make the product as recited in the preamble.

The issue of reference to "cartilaginous matrix" and "bone matrix," has been dealt with above and is now moot.

Regarding failure to mention "osteocytes" and "chondroblasts" in the process steps, Applicants would respectfully point out that patent Specifications are drawn to the level of one of skill in the art and Applicant is not required to burden the Application with extrinsic background material not at all necessary for one of requisite skill to use in practicing the full scope of the invention. It is further assumed that the Examiner, having the requisite skill, must advert to the teachings in the basics sciences involved in a particular invention. In any case, the following is deemed sufficient to clarify the alleged matter.

An osteoblast is a mononucleate cell that is responsible for bone formation. Osteoblasts produce osteoid, which is composed mainly of Type I collagen. Osteoblasts are also responsible for mineralization of the osteoid matrix.

An osteocyte, a star-shaped cell, is the most abundant cell found in bone. Cells contain a nucleus and a thin ring of cytoplasm. **Once osteoblasts become trapped in the matrix they secrete, they become osteocytes.** Osteocytes are networked to each other via long cytoplasmic extensions that occupy tiny canals called canaliculi, which are used for exchange of nutrients and waste.

Chondrocytes are the only cells found in cartilage. They produce and maintain the cartilaginous matrix, which consists mainly of collagen and proteoglycans. **Although chondroblast is still commonly used to describe an immature chondrocyte**, use of the term is discouraged, for it is technically inaccurate since the progenitor of chondrocytes (which are mesenchymal stem cells) can also differentiate into osteoblasts.

A chondroblast is a cell which originates from a mesenchymal stem cell and forms chondrocytes, commonly known as cartilage cells. Chondroblasts that become embedded in the matrix are called chondrocytes..

It is apparent from the above that osteoblasts differentiate into osteocytes when they become traped in the matrix they secret and chondroblast is simply another name for an immature chondrocyte. The Examiner can now appreciate why the process steps of claim 36 advertently did not recite the use of osteocytes and chondroblasts – being required by law to precisely and distinctly claim the subject matter of their invention. With the afore presented clarification, Applicants believe that it is now clear that the process steps of claim 36 will fundamentally lead to the product mentioned in the preamble. As such, withdrawal of

this ground for rejection is respectfully requested.

Claim 68 was also allegedly unclear because it required the connection in claim 36 to be by fibrin adhesion. Applicants respectfully do not see the reason for this confusion but for the fact that the Examiner appears to be improperly discounting the in vitro interlocking area of this invention as not being part of the articulated structure of the claimed product. Claim 68 merely narrowed claim 36 by further claiming that the interlocking area comprises fibrin as an adhesive.

Nevertheless, to advance the prosecution of this invention, Applicants have amended claim 68 to indicate that fibrin adhesion may further be used as a process step in claim 36 to attain the claimed product.

Rejections under 35 U.S.C. 103(a)

Claims 36, 38, 41, 42, 44, 67 and 68, remain rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), in view of Mikos (1996 US Patent 5,522,895; reference A), Rosenthal et al. (1995, U.S. Patent 5, 466, 462, reference B), and Jakob et al. (WO 99/21497; and German-to-English translation).

The Examiner admits that Itay does not teach an *in vitro* composition comprising both cultured cartilage cells and cultured bone cells, said composition comprising cartilage cells on one face thereof and bone cells on the opposing face. The Examiner asserts, however, that Mikos teaches seeding osteoblasts in growth medium onto a biodegradable polymer, allowing the suspension to wick into the polymer foam, and culturing the cells on the polymer to allow them to attach to the foam.

The Examiner further asserts that Rosenthal *et al.* teach that fibrin and polyglycolic acid are functional equivalents in the tissue engineering and wound healing arts.

The Examiner further asserts that Jakob *et al.* teach a composition comprising both a bone side and a cartilage side; the composition of Jakob et al. being a column of tissue that has been removed from a donor site at the articular face of a bone. The Examiner further asserts that Jakob et al. also teach a composition comprising cartilage cells cultured *in vitro* on bone-replacement material.

The Examiner insists that she would construe the transitional phrase, "consisting essentially of" as the open-ended phrase, "comprising" unless the Applicants show that introduction of additional steps or components would materially change the characteristics of Applicants' invention.

The Examiner further claims that the description on page 5 of the specification regarding the definition of "cartilaginous substance" and "bone substance" are not limiting and in the Examiner,

words, "include all non-cellular components of cartilage and bone respectively."

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the *in vitro* bone construct of Mikos and the *in vitro* cartilage construct of Itay to yield a composition comprising cultured cartilage on one side and cultured bone on the opposite side because Jakob *et al.* teach that compositions so configured may be implanted into the articular portions of bones to effectively treat defects. Applicants respectfully disagree and now traverse as follows.

The Combination Asserted by the Examiner is Improper and the "Gist of Applicants' Arguments" is that the Inventors were the first to unobviously produce a functional, biomimetic joint *in vitro*.

Applicants strongly disagree with the propriety of the combination asserted above by the Examiner. The Examiner is arguing that natural tissue grafting as taught by Jakob et. al., obviates as uninventive, any attempt to generate biocompatible tissue or organ *in vitro* merely because the cells that could form part of that *in vitro* tissue or organ have been separately cultured at some point by others. In that sense, why should inventors labor in the field of tissue engineering only for the Examiner to point out that the natural tissue has vitiated their efforts, whereas the main object of such endeavor is to attempt to generate artificial tissue *in vitro?* Naturally the functionality and structure of the natural tissue motivates such endeavor, but that is not the relevant inquiry for patentability purposes; the inquiry is whether a functional joint can be generated *in vitro* and not whether the resulting product looks like the real thing. It is to Applicants' inventive credit, not to their discredit, that their artificial joint mimics Jakob's *et al.'s* natural bone graft. Applicants believe that they were not only the first to do so, but the difficulties in culturing animal cells in the laboratory make the ability to construct a biological joint wholly *in vitro* a highly inventive undertaking.

If the artificial joint looks like the real thing, it is the very inventive genius which Applicants are seeking protection for. After all, it is one of the objects of the instant invention to generate joint-mimetic construct *in vitro* and the ultimate object is to engineer one as close in structure and function to a natural joint as possible. Thus, the relevant inquiry is whether Jakob *et al.* and other cited references in anyway teach, suggest, motivate, or else point to the likelihood of success of an attempt to engineer a functional biological joint *in vitro.*

Nor do the Applicants contend that they are the first to culture bone cells or cartilage cells. Nor do the Applicants suggest that they are the first to realize that animal cells in general are anchorage dependent. Applicants contend, however, that they are the first to culture anchorage dependent osseous and cartilaginous cells suitably anchored on biocompatible materials and arranged in such a manner as to

constitute a novel and unobvious joint construct.

Failure to accord the "Interlocking Area" of the Claims as an Articulated Embodiment of the Claimed Product is Manifestly Erroneous

The Examiner had alleged that it was unclear whether the phrase, "interlockingly connected *in vitro*" to each other was a product limitation and how it changed the scope of the claims. As amended, claim 36 is now in a proper product-by-process format and now explicitly recites an interlocking area being the mating ends of the joint side and the anchor side. As explicitly stated in the specification on page 5, paragraph 4 and on page 6, paragraph 1, the mating ends of the joint side and the anchor side are configured to interlock, preferably in an interdigitating manner. Further, as explicitly stated on page 12, paragraph 1:

> It is essential to the invention that during the connection of bone and cartilaginous component, the carrier material of the bone component is integrated into the cartilage. The resulting construct can now be cultured in vitro, such that the cells are stimulated to adhesion and to the synthesis of their tissue-specific extracellular matrix.

Page 12, paragraph 1. The interlocking area, being as it were, an essential embodiment of the present invention, it is expected that it be accorded all the patentability weight inherent therein.

As now amended, Applicants' in vitro joint construct comprise a joint side, an anchor side, and an interlocking zone for effecting an in vitro integration of both sides in order to in vitro create the functional equivalent of a joint. Support for the interlocking zone may be found in the last paragraph of pages 5 and 11; and Figures 1f and 1g. Applicants believe that if the Examiner would advert her mind to the pages in the Specification where the nature of the interlocking area had been reduced to writing or the figures where it had been reduced to drawings Applicants believe that it would be clear that connecting members are structured in an interdigitating fashion configured to ensure firm connectedness of the two sides.

Applicants believe that anchorage-dependent cartilage and osseous cells may have been grown by others before the date of this invention, Applicants do not believe that a natural organ or tissue being composed of cells provide motivation to preclude the inventiveness of a wholly *in vitro* joint construct aimed at generating in the laboratory, an organ or tissue as close to the natural organ as possible. And even if it were so, the *in vitro* construct of the instant invention differs in material structural respects from the natural joint. For one thing, the interlocking zone mentioned above is a non-natural feature; for another thing, the nerves, gross histological components, connective tissues, and vascularization of a natural joint are lacking in the artificial joint of the present invention, and whereas the artificial joint of the present invention can be used to effect repair of damaged bone, it is nevertheless a man-made joint and should be regarded as such for patentability purposes.

Nor do the Applicants believe that their interlocking bone-cartilage articulating junction approximate its anatomical counterpart. And neither can it reasonably be asserted that the asserted prior art obviated the inventiveness of finding a way, in vitro, to integrally connect the cartilage side and the osseous side in order to engineer an orthopaedically functional joint construct.

To more distinctly claim the invention as an in vitro joint construct, Applicants have deleted the phrase "cartilaginous substance" and "bone substance" and instead replaced them with "cartilaginous substance secreted by the chondrocytes" and "bone substance secreted by the osteoblasts," respectively. Part of the difficulty in advancing the prosecution of this invention is the Examiner's insistence on treating the invention as a composition and her requirement that the Applicants should have listed the entire biochemical composition of the cartilaginous matrix or the bone matrix in order to recite "substance" in a limiting fashion. Applicants are not required to, nor did they attempt to recite the entire histology and gross anatomy of a joint in order for one of skill in this area to appreciate why an in vitro biomimetic joint construct, produced according to the enumerated steps, is fundamentally and inventively different from the natural joint. In very fundamental ways, the process does indeed define the product and the fact that this product is in vitro, without more, patentably separates it from the Jakob construct.

The Claims are now limited to include Cartilaginous Substance and Bone Substance Secreted by the Chondrocytes and Osteoblasts and it is clear error to construe said substances as being co-terminus with their in vivo counterparts

Chondrocytes are the only cells found in cartilage. They produce and maintain the cartilaginous matrix, which consists mainly of collagen and proteoglycans. Applicants believe that there is no other limiting definition of "cartilaginous substance" other than that it consists mainly of collagen and proteoglycans. On the other hand, osteoblasts are mononucleate cell that are responsible for bone formation. Osteoblasts produce osteoid, which is composed mainly of Type I collagen. Osteoblasts are also responsible for mineralization of the osteoid matrix.

Applicants are duly entitled to the Scope-limiting use of "consisting essentially of" and Applicants have met their burden of showing that their product is patentably different from their naturally occurring counterpart being cited as prior art.

Regarding the Examiner's insistence that Applicants have not met their burden of showing that they are entitled to the scope-limiting use of "consisting essentially of" because

they have not shown the basis and novel characteristics of the claimed composition. Applicants respectfully disagree.

In the Response to Office Action filed January 11, 2007, Applicants went into extraordinary detail to show how and why an in vitro joint construct would be anatomically and compositionally different from a natural joint construct. In this case, the bone side of the present invention consists essentially of osteoblasts and tissue-specific extracellular matrix secreted by such cells. Likewise, the cartilage side of the present invention consists essentially of chondrocytes and tissue-specific extra-cellular matrix secreted by chondrocytes. Contrarily, a natural joint like Jakob et al; consists of a physiologically dynamic bone tissue in which osteoblasts are building bone and osteoclasts are resorbing bone. Namely, the bone side of the present invention does not contain osteoclasts as is evident by the process of its making, and thus assuming that the Examiner's asserted combination were proper to begin with, the said combination still fails to account for all the elements of the present invention.

For the records, Applicants have in no way claimed, as erroneously asserted by the Examiner on Page 9 of the Office action, that their *in vitro* construct is identical to Jakob's in vivo bone graft. Applicants have claimed that their *in vitro* joint construct is a biomimetic construct designed to approximate a natural joint as functionally and anatomically as possible in a laboratory setting.

On the basis of the foregoing, Applicants assert that there is no basis for maintaining the obviousness rejection of the instant invention and it is respectfully requested that it be withdrawn.

Claim 37 is rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Goldstein et al. (1999, U.S. Patent 5,962,427: reference C) and Vacanti et al. (1998, U.S. Patent 5,804,178; reference D). Further, claims 39 and 43 are rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Ithay (U.S. 5, 053, 050), Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Wevers (1981, U.S. Patent 4,246,660) and Dunn et al. (1995, Journal of Biomedical Materials Research 29:1363-1371).

Claim 37, 39 and 43, being dependent on claim 36, it is respectfully asserted that the foregoing have adequately addressed this ground for rejection or rendered it moot.

Suffice it to state that the genius of an invention is often a combination of known elements that in hindsight seem preordained. It is improper to use the inventor's patent as an instruction book on how to reconstruct the prior art. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir. 1987). The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the Applicant's disclosure. *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

Applicants respectfully ask that the Examiner to not let hindsight hamper the elegance of the instant wholly-engineered joint construct, if in retrospect, it appears simple enough to the Examiner. Many a Scientists know and appreciate the difficulties of culturing a monolayer of anchorage dependent animal cells of a particular kind, let alone co-culturing animal cells of more than one kind, let alone doing so in a three-dimensional construct, let alone doing so with a structural articulation as complex as a joint. If this invention were obvious, many would have done it because there is a huge orthopedic need for constructs that would accelerate joint healing without the need to graft orthopedic material taken from a different part of the patient's anatomy.

Again, the mere fact that Scientists have grown cells used in the instant invention in the past does not in anyway render obvious the engineering of an organ or tissue comprising those cells.

The Examiner is respectfully asked to reconsider and withdraw these grounds for rejection particularly for the fact that even if the Examiner insists on making these combinations, the combined art still does not meet all the elements of the invention of claim 36. Particularly, the in vitro integration of the joint and the anchor side of the joint construct renders the resulting artificial construct different from any combination which the prior art would teach. As such, it is again respectfully requested that this ground for rejection be withdrawn.

Co-pending Claims

Applicants' counsel is not aware of any co-pending US Patent Application by the inventors setting forth similar subject matter. However, the instant invention has at least one common inventor with the following:

> Patent No. 6703038 - Injectable bone substitute material containing non-ceramic hydroxyapatite cement

Appl. No. 10/716,445 - Injectable bone substitute material (abandoned in 2007).

Should counsel become aware of any patent application responsive to the Examiner's request, it would be made promptly available.

Conclusion

In view of the foregoing remarks, Applicants submit that there is no basis for applying the previous rejections to the pending claims and withdrawal of the rejections is respectfully requested. The claims are believed to be in condition for allowance, and Applicants earnestly solicit from the Examiner early notification of allowability.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, she is invited to contact the undersigned at her earliest convenience.

Respectfully submitted,

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